REMARKS

Reconsideration of the rejection of and/or objection to all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Method claim 1 has been cancelled in order to expedite the prosecution of this application to allowance, with out abandonment or prejudice to Applicants' right to prosecute the cancelled subject matter in one or more continuing applications. Following entry of this amendment, claims 5-14 and 16-19 remain pending in this application.

Claim Status

Independent compound claim 18 currently stands rejected.

Dependent compound claims 5-9, dependent on claim 18, stand rejected.

Dependent compound claims 10-12 have been objected to as being dependent on rejected claim 18, but otherwise have been indicated as being allowable if placed in independent form.

Independent method claim 13 has also been objected to, but has been indicated as being allowable if placed in independent form. Inasmuch as claim 13 is already in independent form, claim 13 will be considered herein as being allowed.

Dependent claims 14 (pharmaceutically acceptable salt), 16 (pharmaceutical composition) and 17 (method), dependent on claim 18, all stand rejected.

Dependent process-for-preparing claim 19, dependent on claim 18, stands rejected.

Claim Rejections – 35 USC § 103

At page 2 of the action, the Examiner states that an "update search yields two references, which raises the following new ground of rejection." However, only one reference is noted and applied to the new rejection, and only one reference was listed in the Notice of References Cited and only one reference copy was provided with the Action. Accordingly, Applicants will assume that the Examiner only intended to refer to a single reference.

Thus, claims 1, 5-9, 14 and 16-19 have been rejected as being obvious over Myers et al. (US 6,645,969 B1), which is hereinafter referred to as "Myers '969" to distinguish from the other Myers et al. references already of record. In supporting this rejection, the Examiner points to certain compounds listed in column 9 and the generic disclosure of column 3, and asserts that Applicants' claimed "method for producing an antiangiogenic and/or vascular permeability reducing effect" is "implicitly" suggested by the Myers '969 reference to its compounds being useful for inhibiting cell proliferation and treating atherosclerosis. In further explanation of this latter assertion, the Examiner states that "it is known in the art that angiogenesis can also cause atherosclerosis by the abnormal growth of epithelial cells in vascular vessels."

This new ground for rejection is respectfully traversed.

It is not clear whether the Examiner appreciates that Myers '969 is identical in substantive disclosure to WO 95/15758, which was previously applied to claim rejections and overcome in this application.

WO 95/15758 was listed in the International Search Report and acknowledged as having been considered by the Examiner's initials on the April 5, 2001 PTO-1449, which was returned with the Action dated May 5, 2002. Myers '969 is a continuation of application No. PCT/US94/14180, which PCT application published as WO 95/15758. The Examiner applied Myers et al. WO 95/15758 to the rejection of original claims 1-17 under section 102, on grounds that the named compound, 4-(3-aminopyrazolyl)-6,7-dimethoxyquinazoline hydrochloride was embraced by the original claims. The Examiner further asserted that Myers taught the use of this compound to treat cellular proliferation and atherosclerosis, which were alleged to be "related to angiogenic and/or vascular permeability."

In response, "use" claim 1 was converted to method form, and narrower compound claim 4 was rewritten in independent form as new compound claim 18, to further distinguish from the Meyer et al. disclosure. Applicants further demonstrated by detailed references to the Meyer et al. disclosure that it did not teach the treatment of cellular proliferation and atherosclerosis. As a result of the amendments to the compound claims, claims 2, 3, 5-12, 14 and 17-19 were allowed. However the rejection of the method claims 1 and 16 was maintained, again on the Examiner's assertion that Myers et al. "reveal that their compounds can treat atherosclerosis – a condition that can be caused by angiogenesis," conclusion that Myers et al. "inherently suggest the treatment of angiogenesis."

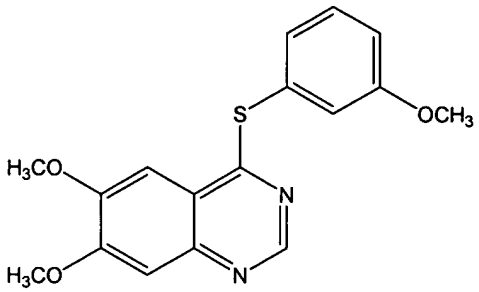
In response, Applicants further limited the compound scope of claim 1. However, based on what appears to have been a misunderstanding, claims 1 and 18 (and claims dependent thereon) were rejected for adding new matter, even though no further amendment had been made to claim 18. The Examiner's misunderstanding with respect to the new matter

has now been straightened out, but nevertheless, previously-allowed claims 5-12, 14, and 17-19 are now rejected under the same Myers et al. disclosure that was previously overcome, except that identical disclosure is not in the form of Myers '969.

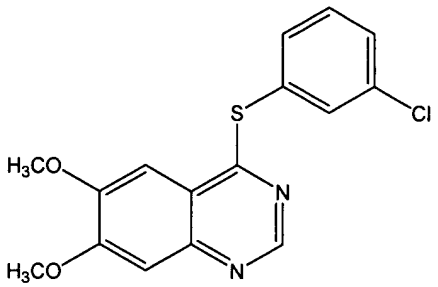
When claims 5-12, 14 and 17-19 were allowed in the Action dated January 29, 2003 over this same Myers et al. disclosure, the Examiner stated that "the teaching of Myers et al. does not disclose species having a substituent on the quinazoline ring in combination with the heterocycle attached to a group equivalent to the instant variable Z." It is understood that the Examiner had reference to the fact that the allowed claims (then and now) have a substituent Zb, which can be only –O- or –S-, linking a heterocyclic ring to the 4-position of the quinazoline ring. On the other hand, the majority of the named compounds in Myers '969 have a phenyl ring at the 4-position of the quinazoline ring and those examples with a 5-or 6-membered heterocyclic ring are not linked via -O- or-S- which are the only values for Zb in claim 18 of the present application. In Myers '969, when ring Ar is a 5- or 6-membered heterocyclic ring it is linked directly to the quinazoline ring or it is linked via a nitrogen atom. In fact Myers '969 teaches away from the 4-position substituent being a 5-6 membered heterocyclic ring in that it states that ring Ar is preferably phenyl or naphthyl (column 4 line 44), preferably phenyl (column 4 line 51).

The Examiner comments at page 3 of the Action that the compounds at lines 54 and 58 of Myers '969, which have a "3-methoxythiophenoxy" and a "3-chlorothiophenoxy" group at the 4-position, respectively, are analogous at this position to presently claimed compounds wherein Zb is –O- and ring C is "thiophene." It is respectfully submitted that this is incorrect. "Thiophenoxy" is the older commonly used term for the group "thiophenyl"

wherein a **phenyl** ring (not a thiophene ring) is linked to the 4-position via sulfur. Thus, the correct structure for the Myers '969 compounds named at column 9, lines 54 and 58 are as follows:



4-(3-methoxythiophenoxy)-6,7-dimethoxyquinazoline



4-(3-chlorothiophenoxy)-6,7-dimethoxyquinazoline

Furthermore the compounds named in Myers '969 have a very limited number of substituents at the 6 and 7-positions of the quinazoline ring, being either 6,7-dihydrogen, 6-chloro and 7-hydrogen, 6,7-dimethoxy or 6,7-dimethyl. None of these combinations of 6- and 7-position substituents falls within the scope of the present claims.

Therefore structurally, the compounds of the present claim 18 are not suggested by the compounds named compounds in Myers '969.

At the generic level, there is a very small area of overlap between present claim 18 and Myers '969. Focusing on the 7-position substituent in particular, the values for R_7 in Myers '969 can be divided up into groups:

Group 1: hydrogen, alkyl, alkoxy, haloalkyl, aralkoxy;

Group 2: cycloalkyl, halo, carboxy, carbalkoxy (or alkoxycarbonyl);

Group 3: alkylthio, hydroxy, aryl.

- The group 1 values are excluded as values for R^2 in the present claims by means of the proviso in claim 18. With regard to aralkoxy, the only aralkoxy value possible in the definition of R^2 is phenoxy, *i.e.*, when R^5 is selected from group 10), R^{29} is phenyl and X^1 is -O- and R^2 cannot be phenoxy per the proviso in claim 18.
- The group 2 values are not values of R^2.
- The group 3 values represent the minor area of generic overlap and the only aryl value in the overlap is phenyl, *i.e.*, when R^5 is selected from group 9) and R^{29} is phenyl.

Therefore the overlap occurs only when the 7-position substituent R^2 is phenyl, hydroxy or C_{1-5}alkylthio (*i.e.*, R^2 is C_{1-3}alkylsulphanyl or R^5X^1 wherein X^1 is -S- and R^5 is selected from group 1) and is C_{1-5}alkyl).

It is respectfully submitted that there is no suggestion or motivation in Myers '969 as a whole that would lead one to combine the necessary parts of the generic teaching so as to make compounds in this minor area of overlap. In fact, the preferences and exemplification in Myers '969 would lead on away from this minor area of overlap. Therefore, the present claims are structurally distinct from the teachings of Myers '969 as a whole, and Myers '969 does not give rise to *prima facie* obviousness.

Method claim 13, which recites only two specific compounds and is in independent form, has already been indicated as allowable. Broad independent claim 1 has been cancelled above (without prejudice), and remaining method claim 17 is dependent on compound claim 18, or narrower compound claims 5-12, which are dependent on claim 18. Therefore, these method claims are patentably distinguished from Myers '969 for the same reasons demonstrated above with respect to compound claim 18. Additionally, Applicants' continue to maintain that these method claims are *further* distinguished from Myers '969 by reason of their method limitation, which is in no way taught by Myers '969. In this regard, the Examiner's attention is drawn to the comprehensive arguments presented in the Amendment and Response of July 29, 2003 at pages 24-25.

Additionally, an implicit or inherent disclosure, *one that is unspoken, cannot* support an obviousness rejection. The Examiner acknowledged in the first Action dated May 6, 2002, that "although Myers et. al. does not explicitly mention angiogenic and/or vascular permeability, their teaching inherently embraced the use claimed herein" (emphasis added). Again, in the present

obviousness rejection, the Examiner states at page 4, "Regarding the '*method for producing an antiangiogenic and/or vascular permeability reducing* effect' of the instant claim 1, the teaching of Myers et. al. implicitly suggests it because the disclosed genus can inhibit cell proliferation, and treat atherosclerosis." An inherent result, one that *will necessarily and inherently occur* when carrying out the teachings of the prior art, can support an *inherent* ***anticipation*** rejection. However, an unspoken, inherent or implicit result *cannot support an* ***obviousness*** *rejection*. Something that is not stated, but rather is implicit or inherent in practicing the prior art, *cannot* provide the necessary motivation for the skilled person to modify that result so as to achieve the claimed invention. Therefore, for this reason as well (and alone), the rejection of the method claims as being obvious over the implicit or inherent effect of the teachings of Myers '969 in inappropriate and should be withdrawn.

The above observations and arguments are believed to be sufficient to demonstrate that the Myers '969 disclosure cannot give rise to a case of *prima facie* obviousness. However, if *prima facie* obviousness is nevertheless asserted, the attached declaration of Stephen Robert Wedge (hereinafter the "Wedge Declaration") makes clear that the exemplified compounds of the present invention that have been tested possess unexpectedly superior properties relative to representative named compounds of Myers '969, that make the present compounds particularly useful for producing an antiangiogenic and/or vascular permeability reducing effect compared to the compounds of Myers '969.

The Table attached to the Wedge Declaration lists tested compounds that are exemplified in the present application, and which fall within the scope of the present claims, as well as two representative compounds named in Myers '969, identified herein as compounds C1 and C2. Compound C1 is the compound named at column 10, line 9 of Myers '969, and compound C2 is the compound named at column 9, line 48.

The test results reported on this Table were determined in accordance with the assays described in the present specification at pages 42-44, which assays are also set out at pages 2-4 of the Declaration. The content of the columns of this Table are described on page 5 of the Wedge Declaration. In summary, columns 1-5 identify the compound tested. Column 6

and 7 report the test results from the "Enzyme Assay" with respect to cFlt and cKDR, which are the cytoplasmic domains of vascular endothelial growth factor receptors Flt1 and KDR respectively. Columns 8 and 9 report the results of the "HUVEC Assay."

The observations of Dr. Wedge with respect to the *in vitro* data provided on this Table are reported in paragraph 7 of the Declaration, beginning at page 6, to which the Examiner's attention is respectfully directed, rather than repeating or attempting to paraphrase those observations herein. From this data and his observations, Dr. Wedge reports that the following conclusions can reasonable be drawn:

> The data indicate that over half of the compounds that were tested in the HUVEC assay show moderate to high activity as *in vitro* inhibitors of VEGF dependent thymidine incorporation, in contrast to the compounds C1 and C2 of US Patent No. 6,645,969, where the HUVEC data qualitatively supports the conclusion that these latter compounds possess no significant activity *in vitro* as inhibitors of VEGF dependent thymidine incorporation.

Conclusion

For the reasons detailed above, Applicants continue to maintain that the presently claimed compounds are structurally distinct from the teachings of Myers '969, and that the claimed method is neither taught nor suggested by the Myers '969 disclosure, any case of *prima obviousness* that might nevertheless be asserted is rebutted and overcome by the data and conclusions reported in the Wedge Declaration. Accordingly, all claims are believed to be in condition for allowance, and a Notice to that effect is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this

application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: November 19, 2004 By: _____

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